

a1 resonance frequency shifts result from changes in the size of said microbubbles and said size changes correspond to changes in hydrostatic pressure in said mammal.

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REMARKS

10 This responds in full to the non-final Official Action mailed March 16, 2000. This response is timely filed by virtue of the enclosed Petition for Extension of Time, extending the time for response through and including September 18, 2000. Reconsideration of this application is respectfully requested in view of the foregoing amendments and the following remarks.

15 By the foregoing amendment, Claims 1 to 5 have been amended to more particularly point out and distinctly claim the subject matter applicants regard as the invention. The amendments to Claims 1 to 5 find support in the application, as originally filed. No new matter has been added. Claims 1 to 5 are currently pending in the present application.

20 In the non-final Office Action mailed March 16, 2000, the Examiner rejected Claims 1 to 5 under 35 U. S. C. §112 as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. The Examiner has rejected Claims 2 and 3 under 35 U.S.C. §102(e) as being anticipated by Miwa et al. (U.S. Patent No. 4,483,345). The Examiner has rejected Claims 1 to 5 under 35 U.S.C. § 102 (e) as being anticipated by Sliwa et al. (U.S. Patent No. 5,749,364). The Examiner has rejected Claims 2 and 4 to 5 under 25 35 U.S.C. §103(a) as being unpatentable over Tickner (U.S. Patent No. 4,265,251) in view of Sliwa, Jr. et al. The Examiner further rejects Claim 1 under 35 U.S.C. §103(a) as being unpatentable over Tickner in view of Sliwa, Jr. et al. and further in view of Schlieff et al. (U.S. Patent No. 5,195,520). Additionally, the Examiner has rejected Claim 4 under 35 U.S.C. §103(a) as being unpatentable over Tickner in 30 view of Sliwa, Jr. et al. and further in view of Miwa. No claim has been allowed.

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Rejection under 35 U.S.C. §112

5 The Examiner has rejected Claims 1 to 5 under 35 U.S.C. § 112, second paragraph, as being indefinite. In Claim 1, Applicants have amended Claim 1 to recite method steps of applying and measuring, and have recited the ultrasound system as transmitting and receiving and have defined the extraction of subharmonic signals in relationship to the fundamental transmit frequency. Claims 2, to 5 have been similarly amended

10 It is the Applicants' belief that claims 1 to 5 are not indefinite, as defined by the second paragraph of 35 U.S.C. §112, and the Applicants respectfully request the withdrawal of the rejection of Claims 1 to 5 under 35 U.S.C. §112, second paragraph.

15 **Rejection under 35 U.S.C. §102(e)**

The Examiner has rejected Claims 2 and 3 under 35 U.S.C. §102(e) as being anticipated by Miwa et al.

20 The Applicants respectfully disagree with Examiner's contention that the referenced teachings anticipate the claimed invention. Miwa et al. teaches use of free bubbles which are generated through ultrasonic cavitation using low-frequency ultrasound waves. (Col. 1, Lines 40-63). These free microbubbles are used for the measurement of hydrostatic pressures according to the critical cavitation pressure. (For example, Col. 11, Lines 1-23). In Miwa, the generation of cavitation
25 bubbles is detected either by higher and lower harmonic ultrasonic waves which accompany such bubbles or by the echo of other ultrasonic waves of higher frequency applied to the region.

While Miwa uses the lower harmonic signals for detecting the existence of cavitation free bubbles, the present invention is based upon the finding of a linear
30 correlation between hydrostatic pressure and amplitude in dB of scattered subharmonic signals from contrast microbubbles. Therefore, the Miwa et al. reference cited by the Examiner fails to anticipate the claimed invention.

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It is the Applicants' belief that Claims 2 and 3 are not anticipated by the Miwa et al. reference, as defined by 35 U.S.C. §102(e), and the Applicants respectfully request that the Examiner withdraw this rejection of Claims 2 and 3 under 35 U.S.C. §102(e).

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Rejection of Claims 1 to 5 under 35 U.S.C. §102(e)

The Examiner rejected Claims 1 to 5 under §102(3) as being unpatentable over Sliwa, Jr. et al. The Examiner states that Sliwa, Jr. uses "an array ... to
10 ensonate contrast agents for harmonic effects with measurement of amplitude and/or frequency changes."

Sliwa, Jr. claims to relate to a novel method of mapping fluid pressure information within a living body utilizing changes in acoustic spectra from microbubbles situated in blood. Sliwa, Jr. et al. teach that differences in the
15 returned acoustic spectra from the microbubbles are related by an algorithm to fluid pressure, which is colorized in a manner similar to Doppler imaging. Unfortunately, no details regarding the procedures of the pressure estimation are given except a formula of the resonant frequency versus the ambient pressure (Col. 2, lines 3-5; similarly, Col. 6, lines 57-59).

20 As to subharmonics, Sliwa, Jr. et al. pointed out that a well-known nonlinear characteristic of resonant bubbles is the generation of super-harmonics and subharmonics. (Col. 2, lines 11-14). They presented an algorithmic expression for frequency f_{nd} (a Doppler frequency shift) versus flow velocity for subharmonics and harmonics. (Col. 6, line 64 – Col. 7, line 4). Although the word subharmonic is
25 mentioned in the patent, nothing regarding the use of subharmonic signals for pressure mapping, as in the present invention, was disclosed.

In summary, the teachings in the Sliwa, Jr. reference fail to anticipate the claimed invention. Sliwa, Jr. et al, discloses no use of subharmonic signals for pressure mapping.

30 It is the Applicants' belief that Claims 1 to 5 are not anticipated by the Sliwa, Jr. et al. reference, as defined by 35 U.S.C. §102(e), and the Applicants

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respectfully request that the Examiner withdraw this rejection of Claims 1 to 5 under 35 U.S.C. §102(e).

5 **Rejection of Claims 2 and 4 to 5 under 35 U.S.C. §103(a)**

 The Examiner has rejected Claims 2 and 4 to 5 under 35 U.S.C. §103(a) as being unpatentable over Tickner in view of Sliwa, Jr. et al. Tickner present a passive ultrasonic technique for pressure determination. In Tickner, the pressure in
10 a liquid is determined from the measured characteristic of sonic signals from the formation of bubbles. (Col. 2, lines 23-31). The Applicants respectfully submit that Tickner, thus, has nothing to do with the use of subharmonic signals from contrast microbubbles for pressure estimation. As noted above, Sliwa, Jr. makes no use of subharmonic signals for pressure mapping

15 The combined teachings of Tickner and Sliwa, Jr. do not render Applicants' invention obvious. Therefore, the claimed invention is a patentably distinct and non-obvious invention.

 It is the Applicants' belief that Claim 2 and 4 to 5 are nonobvious over the Tickner and Sliwa, Jr. references, as defined by 35 U.S.C. §103(a), and the
20 Applicants respectfully request withdrawal of the rejection of Claims 2 and 4 to 5 under 35 U.S.C. §103(a).

Rejection of Claim 1 under 35 U.S.C. §103(a)

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 The Examiner further rejects Claim 1 under 35 U.S.C. §103(a) as being unpatentable over Tickner in view of Sliwa, Jr. et al. and further in view of Schlieff et al. Schlieff teaches that both amplitude and frequency changes may be evaluated in order to ascertain pressure in the medium under test using microbubble scatterers.
30 Schlieff also point out that the n-th harmonic or sub-harmonic frequencies relative to the resonance frequencies can be used. (Col. 2, lines 50-59).

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Obviously, Schliefs approach for pressure measurement via the displacement of the resonance absorption is distinct from the approach of the present invention with the correlation between subharmonic amplitude and pressure. As noted previously, in Tickner, the pressure in a liquid is determined from the measured characteristic of sonic signals from the formation of bubbles. Also, the Sliwa, Jr. reference fail to disclose use of subharmonic signals for pressure mapping as disclosed by Applicants' invention.

The combined teachings of Schliefs, Tickner and Sliwa, Jr. do not render Applicants' invention obvious. Therefore, the claimed invention is a patentably distinct and non-obvious invention.

It is the Applicants' belief that Claim 1 is nonobvious over the Schliefs, Tickner and Sliwa, Jr. references, as defined by 35 U.S.C. §103(a), and the Applicants respectfully request withdrawal of the rejection of Claim 1 under 35 U.S.C. §103(a).

Rejection of Claim 4 under 35 U.S.C. §103(a)

Finally, the Examiner has rejected Claim 4 under 35 U.S.C. §103(a) as being unpatentable over Tickner in view of Sliwa, Jr. et al. and further in view of Miwa. As stated above, in Tickner, the pressure in a liquid is determined from the measured characteristic of sonic signals from the formation of bubbles. Also, the Sliwa, Jr. reference fail to disclose use of subharmonic signals for pressure mapping as disclosed by Applicants' invention. Miwa uses the lower harmonic signals for detecting the existence of cavitation free bubbles, while the present invention is based upon the finding of a linear correlation between hydrostatic pressure and amplitude in dB of scattered subharmonic signals from contrast microbubbles.

The combined teachings of Miwa, Tickner and Sliwa, Jr. do not render Applicants' invention obvious. Therefore, the claimed invention is a patentably distinct and non-obvious invention.

It is the Applicants' belief that Claim 4 is nonobvious over the Miwa, Tickner and Sliwa, Jr. references, as defined by 35 U.S.C. §103(a), and the

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Applicants respectfully request withdrawal of the rejection of Claim 4 under 35 U.S.C. §103(a).

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Thus, it is the Applicants' belief that claims 1-5 are definite, novel, and nonobvious. Prompt consideration and allowance of Claims 1-5 are earnestly solicited.

Should the Examiner determine that any further action is necessary to place this application into even better form, she is encouraged to telephone the Applicants' undersigned representative at the number listed below.

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Respectfully submitted,

William Tao SHI et al.

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Date

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